Notes

Synthesis of 1-β-L-Arabinofuranosylcytosine, the Enantiomer of Cytosine Arabinoside[1]

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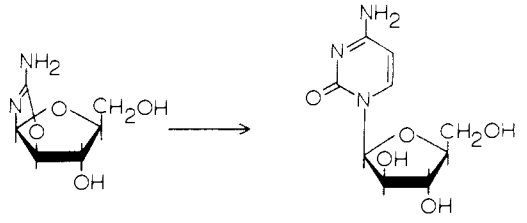
Wu and Chargaff,[2] in a study of the enantiomers of natural nucleosides, have determined that L-uridine is an acceptor for phosphate transfer from carrot phosphotransferase as well as nucleoside phosphotransferase from human prostate. In a similar study using L-adenosine, Shimizu and coworkers[3] have determined that L-adenosine was 50% deaminated in the time that the D enantiomer was completely converted to D-inosine. Snake venom 5′-nucleotidase did not accept L-adenylic acid as a substrate. It is apparent from these examples that enzymes differ widely in their ability to accept L nucleosides as substrates. It was therefore of interest to prepare the enantiomer of the anticancer agent, cytosine arabinoside, since the D enantiomer is known to undergo a rapid enzymatic deamination to form an inactive metabolite, 1-β-D-arabinofuranosyluracil.[4]

An extension of the procedure of Sanchez and Orgel[5] has provided a novel approach to the synthesis of the β-L-nucleoside. Treatment of L-arabinose with cyanamide in MeOH containing concd NH_4OH gave 2-amino-β-L-arabinofurano[1′,2′-4,5]-2-oxazoline (**1**) in good yield. Ring closure of **1** with cyanoacetylene furnished a cyclonucleoside intermediate, which was hydrolyzed, by NH_4OH without isolation, to 1-β-L-arabinofuranosyl cytosine hydrochloride (**2**).

SCHEME I



1 2

Anticancer Evaluation.—Results received to date indicate that **2** possesses no significant activity[6] against lymphoid leukemia L1210 or the Ridgway osteogenic sarcoma.

Enzymatic Investigation.—1-β-L-Arabinofuranosylcytosine·HCl did not function as a substrate in an *Escherichia coli* cytidine aminohydrolase system.[7]

Experimental Section[8]

2-Amino-β-L-arabinofurano[1′,2′-4,5]-2-oxazoline (1).—To a suspension of L-arabinose (30.0 g, 0.2 mole) in MeOH (100 ml) was added cyanamide (16.8 g, 0.4 mole) and concd NH_4OH (10 ml). The stoppered flask has stirred at ambient temp for 24 hr and cooled to 5°, and the solid was filtered and washed with cold *i*-PrOH (24.3 g, 70%). The anal. sample was recrystd from aq MeOH: mp 175° (dec with bubbling), $[\alpha]^{25}D$ + 16.1° (*c* 1.0, H_2O); no uv spectrum above 220 nm. *Anal.* ($C_6H_{10}N_2O_4$) C, H, N.

1-β-L-Arabinofuranosylcytosine (2).—A suspension of **1** (6.96 g, 0.04 mole) in dimethylacetamide (20 ml) was cooled in an ice bath and cyanoacetylene[9] (2.5 ml, 0.04 mole) was added by syringe through a serum cap to the partially evacuated flask. The reaction mixt was allowed to warm to room temp and after 40 min was poured into 1 *N* NH_4OH (100 ml). The soln was heat at 70° for 15 min and the dark mixt was then evapd to dryness *in vacuo*. Two 25-ml portions of MeOH were successively added and evapd *in vacuo*. Addition of 3% dry HCl in MeOH and vol reduction caused crystn. Filtration furnished a crude solid which was recrystd with charcoal from MeOH–EtOAc (7.26 g, 68%). The anal. sample was recrystd from aq *i*-PrOH: mp 197° dec, $[\alpha]^{25}D$ −127.7° (*c* 1.0, H_2O); $\lambda_{max}^{pH\ 1}$ 280 nm (ε 14,000), $\lambda_{max}^{pH\ 7}$ 272 nm (10,700). *Anal.* ($C_9H_{13}N_3O_5 \cdot HCl$) C, H, N.

(1) Synonyms for cytosine arabinoside are: Ara-C, cytarabine, and 1-β-D-arabinofuranosylcytosine.

(2) A. F. Wu and E. Chargaff, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1222 (1969).

(3) B. Shimizu, M. Asai, H. Hieda, M. Miyaki, and H. Okazaki, *Chem. Pharm. Bull.*, **13**, 616 (1965).

(4) R. P. Panzica, R. K. Robins, and L. B. Townsend, *J. Med. Chem.*, **14**, 259 (1971), and ref cited therein.

(5) R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, **47**, 531 (1970); this procedure was employed recently by A. Holy, *Tetrahedron Lett.*, 189 (1971).

(6) The authors with to thank Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center, N.C.I., for the lymphoid leukemia L-1210 evaluation and Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research for the Ridgway osteogenic sarcoma evaluation.

(7) L. I. Pizer and S. S. Cohen, *J. Biol. Chem.*, **235**, 2387 (1960); the authors wish to thank Mr. Randy J. Bauer for the gift of purified *E. coli* cytidine aminohydrolase.

(8) Satisfactory analytical data (C, H, N within ±0.4% of theoretical values) were obtained from MHW Laboratories, Garden City, Mich. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncor. The uv spectra were recorded on a Cary 15 spectrophotometer and optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter.

(9) C. H. Moureu and J. C. Bongrand, *C.R. Acad. Sci.*, **151**, 946 (1910).

Preliminary Studies on the Antitumor Activity of Some Phosphatidyl Nitrogen Mustard Derivatives

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As part of our studies on exploring the use of phospholipid moieties for the potential dual function of transport and latentiation of the bis(2-chloroethyl)-amino group, we synthesized a number of phosphatidyl nitrogen mustard intermediates (**3a–3h**, Table I) following the general procedure of Batrakov, *et al.*,[1] who have synthesized **3c** but did not report on its antitumor activity.[1] Derivatives **3a–3g**, as well as nonlipid synthetic precursors **1** and **2** were tested against leukemia L-1210 in mice[2] and found to afford

(1) S. G. Batrakov, Y. G. Molotovskii, V. V. Dorogov, and L. D. Bergel'son, *Zh. Obshch. Khim.*, **37**, 426 (1967); *Chem. Abstr.*, **67**, 99595 (1969).

(2) Screening data were furnished by Vitro Laboratories, Silver Spring, Md., under contract to the Cancer Chemotherapy National Service Center; **8h** was not available in sufficient quantity for screening.